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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,511	10/31/2003	George Nelson Bennett	61683-00002USPT	3571

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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/699,511	BENNETT ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *May 22, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Amendments of May 17, 2007, have been received and entered in full. Claims 1-7 are pending and under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Response to Amendment

2. The declaration under 37 CFR 1.132 filed May 17, 2007, is insufficient to overcome the rejection of claims 1-7 based upon 35 U.S.C. 103 (a) as set forth in the last Office action because: Applicant's declaration failed to provide persuasive evidence as to unexpected results. It is well established in the art that Cre/Lox recombinase will simultaneously recombine and circularize plasmid DNA. It is therefore not unreasonable to expect success when using Cre/lox to simultaneously recombine and circularize DNA which is attached to a substrate.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watson et al. (Biotechniques, 1997) and Elledge et al. (USPN 5,851,808) in view of Stahl et al. (Biotechniques, 1993).

With regard to claim 1, Watson et al. teach a method of assembling PCR fragments comprising (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment):

a) making a first PCR fragment with first and second primers, wherein the second primer comprises a modified nucleotide that can be removed by a DNA repair enzyme, resulting in a 3' overhang (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment);

b) treating the first PCR fragment with a DNA repair enzyme to generate a 3' overhang

c) making a second PCR fragment with third and fourth primers, wherein the third and fourth primers each comprises a modified nucleotide that can be removed by a DNA repair enzyme resulting in a 3' overhang (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment);

d) treating the second PCR fragment with a DNA repair enzyme to generate a 3' overhang (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment);

e) annealing and ligating the first and second PCR fragments (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment);

f) optionally repeating steps c, d and e until a last PCR fragment is added to the growing chain to produce an assembled fragment (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment),

g) circularizing the assembled fragment (see p. 860 col. 3 under cloning of lac operon fragment, where the fragment is circularized in the vector before transformation)

With regard to claim 2, Watson et al. teach one of the PCR fragments comprises an origin of replication and a selectable marker (see p. 860 col. 3 under cloning of lac operon fragment, the lac operon contains a selectable marker and the vector contains an origion of replication).

With regard to claim 3, Watson et al. teach the first PCR fragment or the last PCR fragment comprises an origin of replication and a selectable marker (see p. 860 col. 3 under cloning of lac operon fragment, the lac operon contains a selectable marker and the vector contains an origion of replication).

With regard to claim 5, Watson et al. teach the nucleotide is deoxyuridine and the DNA repair enzyme is Uracil-DNA-glycosylase followed by T4 endonuclease V (see p. 858 first full paragraph under introduction).

With regard to claims 6 and 7 Watson et al. teach the assembled DNA is greater than 30 kb see p. 860 col. 3 under cloning of lac operon fragment where the lac operon and the vector are greater than 30 kb).

With regard to step (a) of claim 1, Watson et al. do not teach using site specific recombination.

With regard to step (g) of claim 1, Watson et al. do not teach circularization with a site specific recombinase.

With regard to steps (a) and (g) of claim 1, Elledge et al. teach site specific recombination and circularization occurring simultaneously in a single step, with recombinase (see col. 17 lines 44-64, where Elledge teach site specific recombination with cre recombinase *in vitro*. By employing the Cre/lox system for recombination of two plasmids, Elledge necessarily teaches simultaneous circularization and recombination of the plasmid).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of using the cre/lox recombinase system as taught by Elledge with the method of DNA assembly as taught by Watson in order to reduce the time and effort associated with restriction mediated DNA assembly. Elledge et al. teach site specific recombination eliminates the use of restriction enzymes and DNA ligase: instead, these functions are both carried out simultaneously by a single enzyme Cre. Additonally, Elledge teach site specific recombination using Cre in an *in vitro* system. It would have been prima facie obvious to apply the cre/lox recombinase system as taught by Elledge with the method of DNA assembly as taught by Watson in order to have increased efficiency in assembling DNA fragments. The use of cre/lox recombinase system provides for rapid and efficient generation and manipulation of recombinant DNA.

With respect to step (b) of claim 1, Watson et al. and Elledge et al. do not teach immobilizing the PCR fragments for assembly.

With regard to step (g) of claim 1, Watson et al. and Elledge et al. do not teach removing the assembled fragment from the solid support.

Stahl et al. teach immobilizing PCR fragments for assembly (see p. 424 abstract and p. 425 Figure 1).

Stahl et al. teach subsequently removing the assembled gene construct from the bead prior to subcloning (see p. 426 col. 2 first full paragraph).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the step of immobilizing the fragments for assembly as taught by Stahl with the method of DNA assembly as taught by Watson and Liu in order to have a controlled assembly of the fragments. Stahl et al. state, "Immobilization of the first oligonucleotide enables controlled stepwise annealing/ligation of successive 5' phosphorylated oligonucletides to rapidly build up accurate gene constructs making it possible to sub clone for subsequent expression of the gene product (see p. 424 col. 3 first full paragraph)." It would have been prima facie obvious to apply the step of immobilizing the fragments for assembly as taught by Stahl with the method of DNA assembly as taught by Watson and Liu in order to stabilize and control the assembly of the gene constructs. Controlled assembly yields more accurate gene constructs.

Response to Arguments

4. Applicants' arguments filed May 17, 2007, have been fully considered but they are not persuasive.

Applicants argue Watson could not "optionally repeat" the steps "until the last PCR fragment is added to the growing chain to produce and assembled fragment." This argument is not persuasive because Watson generated 3 PCR products and assembled them, therefore the steps used to generate each

product were necessarily repeated as 3 separate PCR products were generated. Additionally, repeating the steps is an option. The instant claims do not require Watson to repeat the steps. Applicants argue Watson does not teach a site specific recombinase or a solid support. This argument is not persuasive because Watson is not relied on for these teachings. The rejection made using Watson was made under 35 U.S.C. 103 (a) therefore Watson is not required to teach each and every limitation of the instant claims.

Applicants argue Elledge does not teach cloning strategies for assembling circularized DNA de novo from assembled PCR fragments nor a solid support. Again Elledge is not relied on for the aforementioned teachings. The rejection made using Elledge was made under 35 U.S.C. 103 (a) therefore Elledge is not required to teach each and every limitation of the instant claims. Elledge was relied on for the teaching of a site specific recombinase, specifically, Cre/lox. Applicants argue Elledge does not teach "simultaneously removing and circularizing." This argument is not persuasive because Elledge is not relied on for the teaching of simultaneously removing and circularizing, however Elledge teach site specific recombination with cre recombinase *in vitro*. By employing the Cre/lox system for recombination of two plasmids, Elledge necessarily teaches simultaneous circularization and recombination of the plasmid. The combination of Stahl and Elledge suggests that using Cre/lox with DNA that is on a solid support would result in the simultaneous removal and circularization of the recombined DNA. An inherent property of Cre/lox is that the upon recombination of the vector and insert the circular vector will re-circularize. If the DNA was bound to a support as in Stahl "simultaneous recombination and circularization would necessarily occur upon removal of the DNA from the support (removal must also occur simultaneously with the recombination and circularization in order for the recombination event to occur).

Applicants argue Stahl does not teach simultaneously removing and circularizing of the vector with the DNA. This argument is not persuasive because again Stahl is not relied on for these teachings.

The rejection made using Stahl was made under 35 U.S.C. 103 (a) therefore Stahl is not required to teach each and every limitation of the instant claims. Again, the combination of Stahl and Elledge suggests that using Cre/lox with DNA that is on a solid support would result in the simultaneous removal and circularization of the recombined DNA. An inherent property of Cre/lox is that the upon recombination of the vector and insert the circular vector will re-circularize. If the DNA was bound to a support as in Stahl "simultaneous recombination and circularization would necessarily occur upon removal of the DNA from the support (removal must also occur simultaneously with the recombination and circularization in order for the recombination event to occur).

Applicants appear to argue this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e., a reasonable expectation of obtaining similar properties. See , e.g. , In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that PCR products can be assembled by Watson. There is further evidence as shown by Stahl that assembly can occur on a solid support. Finally Elledge teaches that Cre recombinase provides simultaneous recombination and circularization of plasmid DNA. This sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In

> others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987); In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the assembly of PCR products by Watson, that assembly can occur on a solid support by Stahl and that Cre recombinase provides simultaneous recombination and circularization of plasmid DNA by Elledge. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the assembly of DNA fragments on a solid support, recombining and circularizing the DNA as discussed in the rejection and as taught by Watson, Elledge and Stahl.

Applicants argue points in the declaration provide by Dr. Bennett, these arguments are not persuasive for the reasons set forth above.

Applicants argue the Examiner misunderstood Applicants comments and Applicants note they did not argue "recombination and circularization occurring in a single step" is inherent to the recombinase, but rather that simultaneous removal and circularization of an assembled DNA from a solid support is inherent.

Finally, Applicants argue simultaneous removal and circularization occur because the DNA was on a solid support and this does not happen in the prior art because the DNA is not on a solid support. This argument is not persuasive because there is strong suggestion in the prior art that the combination of these technologies, specifically assembly of DNA fragments on a solid support and simultaneous removal recombination and circularization of the DNA would be successful. Additionally, the federal circuit held

in *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, __ F.3d __ (Fed. Cir. 2007) a treatment method to be obvious citing the following:

1) *KSR* followed - Confirmation of Stem Cell Properties Obvious: The invention was novel in the sense that it was not confirmed in the prior art that umbilical cord blood is capable of hematopoietic reconstitution. Relying upon *KSR*, the court majority stated that "[w]hile the inventors may have proved conclusively what was strongly suspected before - that umbilical cord blood is capable of hematopoietic reconstitution - and while their work may have significantly advanced the state of the science of hematopoietic transplantations by eliminating any doubt as to the presence of stem cells in cord blood, the mouse experiments and the conclusions drawn from them were not inventive in nature. Instead, the inventors merely used routine research methods to prove what was already believed to be the case. Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention."

Summary

5. No claims were allowable.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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